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Report from the 19th annual Western Canadian Gastrointestinal Cancer Consensus Conference; Winnipeg, Manitoba; 29–30 September 2017

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ABSTRACT

The 19th annual Western Canadian Gastrointestinal Cancer Consensus Conference (WCGCCC) was held in Winnipeg, Manitoba, 29–30 September 2017. The WCGCCC is an interactive multidisciplinary conference attended by health care professionals from across Western Canada (British Columbia, Alberta, Saskatchewan, and Manitoba) who are involved in the care of patients with gastrointestinal cancer. Surgical, medical, and radiation oncologists; pathologists; radiologists; and allied health care professionals participated in presentation and discussion sessions for the purpose of developing the recommendations presented here. This consensus statement addresses current issues in the management of colorectal cancer.

Key Words Colorectal cancer, adjuvant chemotherapy, surgery, molecular tests, immunotherapy, radioembolization, sidedness

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TERMS OF REFERENCE

Purpose

The aim of the Western Canadian Gastrointestinal Cancer Consensus Conference (WCGCCC) is to develop the consensus opinion of oncologists and allied health professionals from across Western Canada, attempting to define best care practices and to improve care and outcomes for patients with gastrointestinal cancers.

Participants

The WCGCCC welcomes medical oncologists, radiation oncologists, surgical oncologists, pathologists, radiologists, gastroenterologists, and allied health professionals from western Canada who are involved in the care of patients with gastrointestinal malignancies (Table I).

Target Audience

The recommendations presented here are targeted to health care professionals involved in the care of patients with colorectal cancer (CRC).

Basis of Recommendations

The recommendations are based on presentation and discussion of the best available evidence. Where applicable, references are cited.

QUESTION 1

What is the optimal duration of oxaliplatin-based adjuvant chemotherapy in node-positive colon cancer?

Recommendations

- For T1–3N1 disease, 3 months of capecitabine and oxaliplatin (CAPOX) treatment is a reasonable option. If using 5-fluorouracil (5FU), leucovorin, and oxaliplatin (FOLFOX), 6 months should remain the standard.
- In "high risk" stage III (T4 or N2 disease), 6 months of oxaliplatin-based treatment is the standard of care.

Summary of Evidence

Treatment with 6 months of fluoropyrimidine–oxaliplatin has been the standard adjuvant treatment for stage III colon

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TABLE I Attendees at the 19th annual Western Canadian Gastrointestinal Cancer Consensus Conference

Name	Position	Organization
Ahmed, Shahid	Medical oncologist	Saskatchewan Cancer Agency
Akra, Mohamed	Radiation oncologist	CancerCare Manitoba
Anderson, Brady	Internal medicine resident	University of Manitoba
Asif, Tehmina	Medical oncologist	Saskatchewan Cancer Agency
Bourque, Sylvie	Medical oncologist	BC Cancer–Fraser Valley Centre
Brigden, Malcolm	Medical oncologist	Jack Ady Cancer Centre
Chalchal, Haji	Medical oncologist	Allan Blair Cancer Centre
Cheung, Kelly	Pharmacist	CancerCare Manitoba
Chornopyski, Tracy	Oncology nurse	CancerCare Manitoba
Chowdhury, Nubia	Oncology nurse	CancerCare Manitoba
Chua, Neil	Medical oncologist	Cross Cancer Institute
Czaykowski, Piotr	Medical oncologist	CancerCare Manitoba
Dehmoobed, Anahita	Pharmacist	CancerCare Manitoba
Deobald, Ray	Surgical oncologist	University of Saskatchewan
Dhalla, Sonny	Surgeon	Brandon Regional Health Centre
Do, Thuan	Medical oncologist	BC Cancer–Fraser Valley Centre
Dueck, Dorie-Anna	Medical oncologist	Saskatchewan Cancer Agency
Dupré, Marc	Pathologist	Diagnostic Services Manitoba
Gill, Sharlene	Medical oncologist	BC Cancer
Gordon, Vallerie	Medical oncologist	CancerCare Manitoba
Graham, Peter	Surgeon	Saskatoon Health Region
Hardy, Edward	Medical oncologist	BC Cancer
Ho, Joel	Internal medicine resident	University of Manitoba
Hunter, William	Radiation oncologist	CancerCare Manitoba
Hyun, Eric	Colorectal surgery fellow	University of Manitoba
Ignacio, Zoe	Oncology nurse	CancerCare Manitoba
Kim, Christina	Medical oncologist	CancerCare Manitoba
King, Karen	Medical oncologist	Cross Cancer Institute
Koski, Sheryl	Medical oncologist	Cross Cancer Institute
Krahn, Marianne	Medical oncologist	CancerCare Manitoba
Le, Lyly	Medical oncologist	BC Cancer
Lee-Ying, Richard	Medical oncologist	Tom Baker Cancer Centre
Liang, William	Internal medicine resident	University of Manitoba
Lim, Howard	Medical oncologist	BC Cancer
Liu, David	Radiologist	University of British Columbia
Loree, Jonathan	Medical oncology fellow	The University of Texas MD Anderson Cancer Center
McGhie, John Paul	Medical oncologist	BC Cancer
Mulder, Karen	Medical oncologist	Cross Cancer Institute
Nashed, Maged	Radiation oncologist	CancerCare Manitoba
Paul, James	Medical oncologist	University of Manitoba and CancerCare Manitoba
Planincic, Elvira	Oncology nurse	Victoria General Hospital
Rivard, Justin	Surgical oncologist	CancerCare Manitoba
Taylor, Marianne	Medical oncologist	BC Cancer
Torri, Vamsee	Medical oncologist	CancerCare Manitoba
Wirtzfeld, Debrah	Surgical oncologist	Winnipeg Regional Health Authority and University of Manitoba
Wong, Ralph	Medical oncologist	CancerCare Manitoba
Yip, Benson	Surgical oncologist	St. Boniface Hospital

cancer since the landmark MOSAIC trial[1] showed that the addition of oxaliplatin to 5FU improved 3-year disease-free survival (DFS) and 10-year overall survival (OS)[1,2]. However, oxaliplatin is associated with cumulative dose-dependent neurotoxicity. Nearly all patients experience some degree of peripheral neuropathy during treatment, which can lead to functional impairment in nearly 45% of patients (31.4% grade 2 and 12.5% ≥grade 3). Peripheral neuropathy can persist long after treatment is complete and in many cases can be permanent, with 30% of patients continuing to experience neuropathy 12 months after completion of adjuvant therapy[3].

The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration was designed to assess whether, to minimize toxicity, the duration of oxaliplatin-based adjuvant chemotherapy could be reduced to 3 months from 6 months without compromising treatment efficacy[4]. A prospectively planned pooled analysis, IDEA considered six concurrent international trials involving 12,834 patients, including TOSCA, SCOT, IDEA France, HORG, C80702, and ACHIEVE. The primary endpoint was the noninferiority of 3 months compared with 6 months of oxaliplatin-based adjuvant chemotherapy (CAPOX or FOLFOX) in stage III colon cancer, with an upper-bound noninferiority margin of 12% for DFS (HR: 1.12). All stage III colon cancer patients randomized in the trials were included in the primary analysis, but several of the trials included a second randomization to address additional research questions. For example, the Alliance C80702 trial included a randomization to compare celecoxib with placebo after completion of FOLFOX, and the TOSCA trial had a secondary randomization to bevacizumab, which was eventually dropped. In addition, some trials included stage II patients (TOSCA, SCOT, and HORG), and SCOT also included rectal cancers, although the primary analysis focused on patients with stage III colon cancer.

At the American Society of Clinical Oncology 2017 annual general meeting, the primary analysis of the IDEA collaboration was shown to be negative because the upper bounds of the confidence interval passed the acceptable pre-specified noninferiority margin (DFS HR: 1.07; 95% CI: 1.00 to 1.15)[4]. The 3-year DFS was 74.6% for the 3-month course compared with 75.5% for the 6-month course. Depending on treatment received (CAPOX or FOLFOX), grade 2 or greater peripheral neuropathy was reduced to 15%–17% for 3 months of therapy compared with 45%–58% for 6 months of therapy ($p < 0.001$).

The IDEA collaboration included multiple pre-planned subgroup analyses. Specifically, the authors planned to assess subgroups stratified by N stage, T stage, chemotherapy regimen (FOLFOX vs. CAPOX), age (<70 years vs. >70 years), and tumour sidedness. When comparing outcomes based on regimen, patients who received FOLFOX did not meet the cut-off for noninferiority (HR: 1.16; 95% CI: 1.06 to 1.26); those who received CAPOX did (HR: 0.95; 95% CI: 0.85 to 1.06). The difference in outcome based on regimen was confirmed with an interaction test ($p = 0.0051$). Those results were driven largely by the SCOT trial, which contributed more than half the CAPOX-treated patients to the full analysis and which also met its primary endpoint of demonstrating that 3 months of adjuvant oxaliplatin-based therapy was noninferior to 6 months of therapy (HR: 1.006; 95% CI: 0.909 to 1.114; $p = 0.012$)[5].

Since the presentation of those data, there has been debate about how to interpret the stratification based on treatment regimen given that patients were not randomized according to type of chemotherapy. There was no suggestion that the patients who received CAPOX had more favourable baseline or disease characteristics. The increased efficacy of a capecitabine-containing regimen might be related to the continuous administration of capecitabine for 2 of 3 weeks, to the earlier exposure to higher doses of oxaliplatin, or perhaps to something inherent to the pharmacology of capecitabine.

Similarly, in the X-ACT trial, adjuvant capecitabine and 5FU were shown to be equivalent for DFS ($p < 0.0001$) and OS ($p = 0.0001$), but a trend toward superiority for capecitabine was observed for both endpoints ($p = 0.068$ and $p = 0.060$ respectively)[6]. Other data suggest that 3 months of continuous exposure to 5FU is superior to 6 months of bolus 5FU[7], and retrospective data suggest that CAPOX might be more active than FOLFOX in stage III colon cancer[8].

With respect to the subgroup analyses based on T and N stage, no single T or N stage met the noninferiority criteria; however, the authors of the IDEA collaboration performed an unplanned analysis of low-risk (T1–3N1) compared with high-risk (T4 or N2) groups. In that analysis, which pooled the CAPOX and FOLFOX groups, the result in the low-risk group met the criterion for noninferiority (HR: 1.01; 95% CI: 0.90 to 1.12), but the result in the high-risk group was clearly inferior (HR: 1.12; 95% CI: 1.03 to 1.23). When the authors assessed those risk groups stratified by type of chemotherapy, neither CAPOX nor FOLFOX was noninferior in the high-risk group. In the low-risk group, CAPOX (HR: 0.85; 95% CI: 0.71 to 1.01), but not FOLFOX (HR: 1.10; 95% CI: 0.96 to 1.26), was noninferior. The statistical plan for the trial did not include those low- and high-risk groups as part of the pre-specified analysis, and so the *post hoc* nature of those results should be interpreted with caution. The large sample size and pragmatic nature of the groupings do, however, provide support for the interpretation.

Taking into account all the evidence, the results of the IDEA pooled analysis support a risk-based approach to patients with node-positive colon cancer. For patients with high-risk disease (T4 or N2), 6 months of oxaliplatin-based adjuvant therapy remains the standard of care. For patients with low-risk disease (T1–3N1), 3 months of adjuvant CAPOX treatment is a reasonable option to consider. If using FOLFOX, 6 months of therapy remains the standard of care for all risk groups.

QUESTION 2

What is the optimal timing of surgery after neoadjuvant chemoradiation therapy in patients with clinical stage II or III rectal cancer?

Recommendations

- The optimal timing of surgery after neoadjuvant chemoradiation therapy in patients with clinical stage II and III rectal cancer is not known.

- Surgery should be considered between 6 and 10 weeks after completion of chemoradiation in patients with clinical stage II or III rectal cancer.

Summary of Evidence

In the German rectal cancer study that demonstrated a benefit with neoadjuvant chemoradiation, surgery took place 6 weeks after completion of the chemoradiation[9]. However, studies have suggested that a pathologic complete response (pCR) after neoadjuvant chemoradiation is associated with improved DFS and OS[10,11]. A recent meta-analysis suggested that increasing the interval between completion of neoadjuvant chemoradiation and surgery to more than 6–8 weeks significantly increased the rate of pCR without any increase in detrimental outcomes[12]. Since publication of that meta-analysis, other large retrospective series have also demonstrated an increase in pCR rates with a longer interval from completion of chemoradiation to surgery[13–15]. Peak pCR rates were seen when surgery occurred between 9 and 12 weeks after completion of neoadjuvant therapy, although one study noted an increase in circumferential radial margin involvement if surgery occurred more than 12 weeks after completion of the chemoradiotherapy[13–15].

The GRECCAR-6 trial is the only prospective randomized controlled trial that was designed to evaluate the pCR rate with an increased interval between completion of neoadjuvant therapy and definitive surgery[16]. That multicentre trial randomized patients with clinical T3–4 or Tx node-positive tumours of the mid- or lower rectum to surgery either 7 or 11 weeks after completion of neoadjuvant chemoradiation. No difference in the primary endpoint of pCR was observed between the two groups (15.0% in the 7-week group vs. 17.4% in the 11-week group, $p = 0.5983$). In both groups, the pCR rate was as high or higher than the pCR rates reported in retrospective studies. In terms of secondary outcomes, complete total mesorectal excision specimens were obtained more often in the 7-week group (90% vs. 79%, $p = 0.0156$). Although no difference in anastomotic complications was observed, differences in medical complications were evident, mostly because of more urinary complications in the 11-week group. A longer wait time between completion of neoadjuvant chemoradiation and surgery was not associated with an increase in synchronous metastatic disease (2.3% in the 7-week group vs. 1.5% in the 11-week group, $p = 1.00$). The results of the study suggest that waiting longer between the completion of neoadjuvant therapy and surgery is not associated with an improvement the pCR rate and might be associated with increased morbidity; however, the results are far from indisputable. The optimal timing for surgery after completion of neoadjuvant chemoradiation for stages II and III rectal cancer remains unclear. Based on the data, surgery should be considered between 6 and 10 weeks after completion of chemoradiation.

QUESTION 3

What is the current role for nonsurgical management of rectal cancer after a complete clinical response (cCR) to neoadjuvant chemoradiation therapy?

Recommendations

- The standard approach for patients after a cCR is definitive surgical resection.
- If being considered for a nonsurgical approach, patients should be considered for a clinical trial if available.
- In patients who do not undergo resection, an intensive surveillance strategy is required. The case must be presented at a multidisciplinary case conference.

Summary of Evidence

Patients with clinical T3–4 or node-positive rectal cancer are often treated with upfront chemotherapy and radiation, followed by radical surgery and further postoperative chemotherapy[9,17]. A cCR after neoadjuvant chemoradiotherapy occurs in 20%–30% of cases[18,19]; however, rates of pCR after neoadjuvant chemoradiotherapy range from 10% to 20%[20,21].

Generally, patients who experience a pCR in response to induction therapy have a good long-term outcome[21]. The question therefore arises whether selected patients with a cCR might be spared surgical resection. A number of institutional reports provide insight into the long-term outcomes of patients managed using a nonsurgical approach. The Habr-Gama group in Brazil published data for patients who received long-course neoadjuvant chemoradiation for rectal cancer, 20% of whom had clinical T2N0 disease at baseline. Those who experienced a cCR, as determined by physical examination, endoscopy, and cross-sectional imaging, were managed with close observation[22]. At almost 5 years of follow-up, recurrence rates were low (13%), and although 5% of recurrences were local, all were able to be managed with salvage surgery[23]. In patients managed with close observation, the 5-year OS was 93%, and the DFS was 85%. However, a recent publication showed that local recurrence-free survival was significantly worse in patients with baseline clinical T3–4 tumours than in those with clinical T2 tumours (69% vs. 96%, $p = 0.009$)[24].

Other small case series have also shown promising outcomes for patients managed with a nonsurgical approach. In a series of Dutch patients with a cCR (determined clinically and endoscopically, and with magnetic resonance imaging and biopsy) who underwent close observation, the 3-year local regrowth-free survival was 86%[25]. Patients from the Memorial Sloan Kettering Cancer Center who experienced a cCR were compared with a group of control patients who experienced a pCR: recurrence rates were low in both groups[26]. A propensity score–matched analysis of patients in Manchester who underwent chemoradiotherapy followed by observation revealed no difference in the 3-year OS between those who underwent observation and those who underwent surgical resection. Of those who were observed, 34% experienced local regrowth, with 88% of those cases being amenable to surgical resection[27].

A number of factors make it difficult to select candidates for non-operative management from among the patients who achieve a cCR. The definition of a cCR differs in various reported series, and it is difficult to determine which patients with a cCR will also experience a pCR. In patients who experience a cCR as assessed by digital rectal examination and proctoscopy, up to 75% might have residual

tumour found on pathology examination[19]. Currently no imaging modality has been shown to reliably predict pCR[28–33]. Also, in patients who do not undergo standard surgical resection, there is a possibility that curative surgery might not be an option upon recurrence[34].

Although the data for non-operative management are promising, prospective clinical trials are necessary before such an approach can be recommended in patients who experience a CCR in response to neoadjuvant chemoradiotherapy. The results of the prospective NCT01047969 trial (https://clinicaltrials.gov/ct2/show/NCT01047969) will add further information. For now, surgical resection remains the standard of care. If a patient declines surgical intervention or is medically unfit for major surgery, their case should be discussed in a multidisciplinary case conference. Ideally, non-operative approaches should occur in the setting of a prospective clinical trial, if available. In patients who opt for a nonsurgical approach, close and frequent monitoring should occur. No guidelines discussing how to follow those patients have been published; however, an intensive surveillance strategy should include frequent history, physical examination, endoscopy, and cross-sectional imaging (computed tomography and magnetic resonance imaging).

QUESTION 4

What molecular tests should now be the standard of care for patients with newly diagnosed CRC?

Recommendations

- Mismatch repair (MMR) testing should be performed in all CRC patients for Lynch syndrome ascertainment and for predictive and prognostic factors.
- Extended *RAS* and *BRAF* testing should be performed in patients with metastatic disease being considered for therapy.
- Other biomarkers currently remain investigational.

Summary of Evidence

In CRC, molecular testing can inform tumour classification, pathogenesis, prognosis, and prediction of response to specific therapies. Tumour mismatch repair (MMR) protein status, microsatellite instability (MSI) status, and *BRAF* and *KRAS/NRAS* mutation status are the most commonly sought molecular tests for CRC.

Testing for MMR allows for the identification of MMR-deficient (dMMR) CRC, either hereditary (Lynch syndrome secondary to germline mutations) or sporadic in nature. In CRC, dMMR produces MSI through DNA replication errors, and MSI-high (MSI-H) CRCs are associated with improved DFS and OS[35]. Unlike Lynch syndrome–associated CRC, sporadic dMMR tumours are associated with *BRAF* V600E mutations and typically present as right-sided tumours in older female patients[36,37]. Although clinical features and some tumour morphology features can help to identify dMMR and MSI-H tumours, those approaches lack sensitivity. Immunohistochemical (IHC) testing for MMR expression has become widespread in recent years and is currently used primarily for screening for Lynch syndrome. The standard 4-antibody MMR IHC panel incorporates *MLH1, MSH2, MSH6,* and *PMS2* testing and has sensitivity and specificity exceeding 90% for the detection of dMMR tumours[38]. Mismatch repair IHC testing is highly concordant with polymerase chain reaction–based MSI testing[38,39].

In select cases of early-stage CRC, MMR status can provide information that assists in decision-making for adjuvant chemotherapy. Retrospective analyses suggest that single-agent fluoropyrimidine therapy might be ineffective in dMMR or MSI-H CRCs[40–42]; MMR or MSI status could therefore influence whether adjuvant therapy consists of observation alone, single-agent fluoropyrimidine therapy, or oxaliplatin-based doublet chemotherapy after surgical resection for stage II colon cancers. Furthermore, recent data suggest that MMR and MSI status can identify patients with metastatic CRC who might benefit from immunotherapy (see Question 5).

Selective, aged-based MMR testing is advocated as a cost-effective process for Lynch syndrome screening, but only universal testing is able detect all sporadic dMMR or MSI-H cancers[43]. Testing for MMR is therefore recommended in all patients with CRC, because it helps to identify Lynch syndrome and provides prognostic[44] and predictive information.

In CRC, *BRAF* V600E mutations are common; they are identified in approximately 10% of all CRCs, 60% of sporadic dMMR tumours, and approximately 8% of advanced CRCs[45–48]. A *BRAF* V600E mutation in metastatic CRC is associated with worse progression-free survival (PFS) and OS, and a decreased response to anti-EGFR agents[37,46,47,49]. More than half of all CRCs harbour mutations in *KRAS, NRAS,* and *BRAF;* only a small proportion of CRCs have mutations in both *RAS* and *RAF*[50]. Improved PFS and OS are expected for patients with wild-type (WT) *KRAS* and *BRAF* metastatic CRCs treated with EGFR-targeted therapies[51]. In the setting of MLH-1–deficient tumours, the presence of a *BRAF* mutation excludes a Lynch syndrome–related cancer[44]. Testing for *BRAF* V600E and *KRAS* mutations can be performed by polymerase chain reaction. Recently, IHC clones that detect the *BRAF* V600E protein product have become commercially available. When fully optimized, IHC with the VE1 clone has sensitivity and specificity exceeding 90% for the detection of the *BRAF* V600E protein product[52]. Because the tests provide information about response to anti-EGFR therapies and screen for Lynch syndrome, it is recommended that patients with metastatic CRC undergo testing for *KRAS/NRAS* and *BRAF*[44]. Other biomarkers remain investigational at this point in time.

QUESTION 5

What is the role of immunotherapy in patients with metastatic CRC?

Recommendations

- Use of a PD-1 inhibitor (nivolumab or pembrolizumab) is a reasonable option in patients with stage IV MSI-H or MMR-deficient CRC after treatment failure with, or intolerance to, fluoropyrimidine, oxaliplatin, and irinotecan.
- In MMR-proficient tumours, single-agent nivolumab or pembrolizumab has been shown to be ineffective and should not be used.

Summary of Evidence

The distinct subset of MSI-H CRCs is distinguished by a hypermutable state, increased neoantigen load, and tumour-infiltrating lymphocytes. Although such tumours constitute only 3%–4% of all metastatic CRCs, the foregoing characteristics suggest that they might respond to checkpoint inhibitors.

In 10 patients with dMMR CRCs, Le *et al.*[53] demonstrated that the PD-1 inhibitor pembrolizumab resulted in an overall response rate (ORR) of 40% and a disease control rate (DCR) of 90%. Responses tended to be quick and prolonged. Pembrolizumab was well tolerated, with few grade 3 or 4 toxicities reported. In patients with MMR-proficient tumours, the response rate was 0%. Those results were confirmed in the KEYNOTE-164 study, which showed an ORR of 28% and a DCR of 51% in 61 patients with MSI-H tumours treated with pembrolizumab[54,55].

The PD-1 inhibitor nivolumab has also shown promising activity. The CheckMate 142 study was a nonrandomized phase II trial of nivolumab in heavily pretreated patients with MSI-H CRC[56]. Patients in the first arm received nivolumab 3 mg/kg every 2 weeks, and patients in the second arm received a combination of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 cycles, followed by nivolumab 3 mg/kg every 2 weeks until progression. In the 74 patients who received nivolumab monotherapy, the ORR and DCR were 36% and 74% respectively[56]. The therapy was well-tolerated, with few grade 3 or 4 toxicities. Recently, the results of the combination therapy arm were published, showing an impressive 55% ORR and 88% DCR[57]. Grade 3 or 4 toxicities occurred in 32% of patients, with diarrhea, fatigue, and pruritus being the most frequent adverse events reported. The response rates with combination immunotherapy appear to be higher, but because of the nonrandomized nature of the trial, a direct comparison between the two arms is not possible.

In 2017, pembrolizumab and nivolumab were both approved by the U.S. Food and Drug Administration for patients with MSI-H or dMMR metastatic CRC experiencing progression after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. At the time of the present review, no HC Notice of Compliance had been issued for pembrolizumab or nivolumab in this setting.

To summarize, a small (3%–4%) subset of CRC patients appears to derive substantial benefit from checkpoint inhibitors. The benefits are marked and therefore PD-1 inhibitors should be offered to this select group of patients.

QUESTION 6

What are the indications for radioembolization in patients with metastatic CRC?

Recommendations

- There is no survival benefit with the use of radioembolization in patients with metastatic CRC, and its use should not be considered in the first-line setting unless part of a clinical trial.

Summary of Evidence

The prognosis of patients with CRC and liver metastasis is determined largely by the degree of liver infiltration by tumour. The rationale for, and use of, liver-directed therapies such as surgical resection or ablation for the treatment of resectable or potentially locally curative liver metastases was, despite high rates of recurrence within the liver, established in population-based cohorts and randomized controlled trials[58,59]. A recent randomized phase II trial of patients with CRC and unresectable liver-limited metastases revealed that, at a median follow-up of 9.7 years, compared with chemotherapy alone, chemotherapy plus local treatment with radiofrequency ablation, with or without resection, achieved a significant improvement in OS (HR: 0.58; 95% CI: 0.38 to 0.88, $p < 0.01$)[60]. However, that study had methodology limitations that make the results difficult to interpret. The study was initially designed as a phase III trial, with OS as the primary endpoint. But accrual was slower than expected, and the study was amended to a phase II trial with a smaller sample size and a primary endpoint of a 30-month OS rate exceeding 38% in the combined-modality arm. Secondary endpoints included PFS and OS. At the time of the initial report, a statistically significant difference in PFS was observed between the two arms (16.8 months for patients in the combined-modality arm vs. 9.9 months in the chemotherapy-only arm, $p = 0.025$), but no difference in OS[61]. Systemic treatment initially consisted of FOLFOX4. After 2005, bevacizumab was added, and in both arms, according to protocol, chemotherapy was required to be given for 6 months only. Although the results are encouraging, the study sample consisted of highly selected patients who experienced an impressive median OS in both groups (45.6 months for the combined-modality group vs. 40.5 months in the chemotherapy-only arm), and the use of locoregional therapies in patients with incurable CRC remains unclear.

The use of selective internal radiation therapy (SIRT) that uses resin-coated microspheres loaded with the therapeutic radioisotope yttrium-90 has demonstrated encouraging results in terms of DCR[62] and depth of response[62,63]. Those results have been reiterated in small studies in the third line or in chemorefractory disease[64], in the second line[65], and in the earlier first line[66] for patients with liver-dominant metastatic CRC. The SIRFLOX and FOXFIRE family of studies was designed as a series of multinational trials to determine whether, compared with systemic chemotherapy alone, radioembolization with yttrium-90 resin microspheres (SIR-Spheres: Sirtex Medical, Sydney, Australia) in combination with systematic chemotherapy resulted in an improvement in OS in the first-line treatment of patients with metastatic CRC with unresectable liver metastases[67]. Despite a higher proportion of patients achieving a tumour response and improved liver-specific PFS, the aggregated studies failed to achieve the primary outcome of improvement in OS with the addition of SIRT to chemotherapy (HR: 1.04; 95% CI: 0.90 to 1.19; $p = 0.61$). The groups showed no difference in overall PFS or the rate of conversion to a surgically resectable scenario. Notably, rates of conversion to surgical resection were lower than expected in both arms, possibly related to the high incidence of an intact primary (17% in the SIRT-plus-chemotherapy arm vs. 16% in the chemotherapy-only arm) and the presence of extrahepatic metastatic disease[63]. The most common grade 3 or

4 adverse event was neutropenia, which occurred in 37% of patients who received SIRT plus chemotherapy and in 24% of patients who received only chemotherapy. Increased rates of thrombocytopenia, abdominal pain, and fatigue were also seen with SIRT plus chemotherapy compared with chemotherapy alone. Technical considerations related to the radioactivity dosing schema, biomarkers, catheter placement, and site of actual administration were not fully explored; however, by nature, the SIRT procedure requires a high degree of technical expertise. Adverse events of gastrointestinal toxicities might have been attributable to a lack of experience on the part of the interventional radiologists performing the procedure in an earlier phase of the study, with no roll-in period[68].

A *post hoc* analysis of the SIRFLOX and FOXFIRE studies suggests that patients with right-sided primary tumours experienced an OS benefit with SIRT plus chemotherapy compared with chemotherapy alone (median OS: 22 months vs. 17 months). The presence of a right-sided primary has been associated with worse prognosis[58,69] and therefore warrants further investigation.

Based on the data, the addition of SIRT to chemotherapy in the first-line treatment of unselected patients with metastatic CRC is not recommended. Outside of a clinical trial setting, SIRT should not be used in the first-line setting of metastatic CRC with liver metastases. If SIRT is being considered in the chemotherapy-refractory setting, the patient's case should be discussed in a multidisciplinary case conference setting.

QUESTION 7

Does sidedness matter in advanced colon cancer?

Recommendations

- Right-sided tumours are genomically different from left-sided tumours. That difference can affect the use of biologic and chemotherapy strategies. Prognosis is poorer in right-sided tumours, which might not respond well to EGFR-directed therapies.

Summary of Evidence

Cancers of the right side of the colon (cecum, ascending colon, hepatic flexure, and transverse colon) differ on a molecular level from cancers of the left side of the colon (splenic flexure, and descending and sigmoid colon). The molecular differences between right- and left-sided CRCs might be related to their different embryologic origins, given that the right colon originates from the midgut, and the left colon develops from the hindgut.

It is possible that tumour location is simply a marker for molecular biology. *BRAF* and *KRAS* mutations and hypermethylation occur more commonly in right-sided tumours; left-sided tumours are more likely to be non-mutated[70,71]. Gene expression profiling has led to the identification of 4 consensus molecular subtypes (CMS) of CRC[72]:

- CMS1 tumours tend to display MSI, CpG island methylator phenotype, hypermethylation, and *BRAF* mutation.
- CMS2 (canonical type) tumours have high somatic copy number alterations and Wnt and Myc activation.
- CMS3 tumours have low CpG island methylator phenotype and somatic copy number alterations, together with mixed MSI status.
- CMS4 (mesenchymal type) tumours are associated with high somatic copy number alterations, angiogenesis, stromal infiltration, and activation of transforming growth factor β.

The CMS type appears to be associated with tumour location and prognosis. The CMS1 type tends to occur more frequently in women with right-sided tumours and are associated with worse prognosis upon relapse. In contrast, CMS2 tumours tend to be left-sided and associated with better prognosis. The CMS4 tumours are associated with worse relapse-free survival and OS.

Retrospective analyses of randomized clinical trials confirm that tumour sidedness is associated with prognosis, even in *RAS* WT tumours. Among the 370 patients from the CRYSTAL and FIRE-3 trials who had *RAS* WT metastatic CRC, PFS and OS were superior for the patients with left-sided tumours compared with the patients with right-sided tumours, although the number of patients with right-sided tumours was small in both studies (33 and 28 respectively)[73]. A number of other retrospective analyses[74,75] and meta-analyses[74–76] support the finding that tumour sidedness is prognostic.

Furthermore, recent data[75,76] suggest that tumour sidedness might be predictive, because patients with *RAS* WT left-sided tumours experience superior survival when an EGFR-directed antibody is added to chemotherapy. The Cancer and Leukemia Group B/SWOG 80405 study compared the addition of cetuximab or bevacizumab to 5FU-based chemotherapy, showing no difference in median OS (30 months with chemotherapy–cetuximab vs. 29 months with chemotherapy–bevacizumab; HR: 0.88; 95% CI: 0.77 to 1.01; $p = 0.08$)[77]. However, when the data were retrospectively examined to assess the effect of primary tumour location in patients with *RAS* WT, those with left-sided tumours experienced a greater OS benefit from chemotherapy–cetuximab than from chemotherapy–bevacizumab (median OS: 36 months vs. 31.4 months), and those with right-sided tumours experienced better survival with chemotherapy–bevacizumab than with chemotherapy–cetuximab (median survival: 24.2 months vs. 16.7 months)[78]. A meta-analysis of randomized controlled trials has since confirmed that, in patients with *RAS* WT left-sided colon cancer, survival is improved with the use of EGFR-directed therapy plus chemotherapy compared with the use of bevacizumab plus chemotherapy. In contrast, patients with right-sided colon cancer do not receive the same benefit from EGFR-directed therapy and seem to do better with chemotherapy–bevacizumab[76]. Although results have consistently suggested that tumour sidedness is predictive of response to EGFR-directed therapy plus chemotherapy, the analyses have all been retrospective in nature and should be interpreted with caution. Prospective data are eagerly awaited.

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CONFLICT OF INTEREST DISCLOSURES

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REFERENCES

1. Andre T, Boni C, Mounedji-Boudiaf L, *et al.* on behalf of the MOSAIC investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350:2343–51.
2. Andre T, de Gramont A, Vernerey D, *et al.* Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to *BRAF* mutation and mismatch repair status of the MOSAIC study. *J Clin Oncol* 2015;33:4176–87.
3. Andre T, Boni C, Navarro M, *et al.* Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009;27:3109–16.
4. Shi Q, Sobrero AF, Shields AF, *et al.* Prospective pooled analysis of six phase III trials investigating duration of adjuvant (adjuv) oxaliplatin-based therapy (3 vs 6 months) for patients (pts) with stage III colon cancer (CC): the IDEA (International Duration Evaluation of Adjuvant chemotherapy) collaboration [abstract LBA1]. *J Clin Oncol* 2017;35:. [Available online at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.18_suppl.LBA1; cited 8 June 2018]
5. Iveson T, Kerr R, Saunders M, Hollander N, Tabernero J, Haydon A. Final DFS results of the SCOT study: an international phase III randomised (1:1) non-inferiority trial comparing 3 versus 6 months of oxaliplatin based adjuvant chemotherapy for colorectal cancer [abstract 3502]. *J Clin Oncol* 2017;35:. [Available online at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.3502; cited 5 June 2018]
6. Twelves C, Scheithauer W, McKendrick J, *et al.* Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. *Ann Oncol* 2012;23:1190–7.
7. Chau I, Norman AR, Cunningham D, *et al.* A randomised comparison between 6 months of bolus fluorouracil/leucovorin and 12 weeks of protracted venous infusion fluorouracil as adjuvant treatment in colorectal cancer. *Ann Oncol* 2005;16:549–57.
8. Loree JM, Mulder KE, Ghosh S, Spratlin JL. CAPOX associated with toxicities of higher grade but improved disease-free survival when compared with FOLFOX in the adjuvant treatment of stage III colon cancer. *Clin Colorectal Cancer* 2014;13:172–7.
9. Sauer R, Becker H, Hohenberger W, *et al.* on behalf of the German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731–40.
10. Zorcolo L, Rosman AS, Restivo A, *et al.* Complete pathologic response after combined modality treatment for rectal cancer and long-term survival: a meta-analysis. *Ann Surg Oncol* 2012;19:2822–32.
11. Yeo SG, Kim DY, Kim TH, *et al.* Pathologic complete response of primary tumor following preoperative chemoradiotherapy for locally advanced rectal cancer: long-term outcomes and prognostic significance of pathologic nodal status (KROG 09-01). *Ann Surg* 2010;252:998–1004.
12. Petrelli F, Sgroi G, Sarti E, Barni S. Increasing the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer: a meta-analysis of published studies. *Ann Surg* 2016;263:458–64.
13. Kwak YK, Kim K, Lee JH, *et al.* Timely tumor response analysis after preoperative chemoradiotherapy and curative surgery in locally advanced rectal cancer: a multi-institutional study for optimal surgical timing in rectal cancer. *Radiother Oncol* 2016;119:512–18.
14. Rombouts AJM, Hugen N, Elferink MAG, Nagtegaal ID, de Wilt JHW. Treatment interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer patients: a population-based study. *Ann Surg Oncol* 2016;23:3593–601.
15. Probst CP, Becerra AZ, Aquina CT, *et al.* on behalf of the Consortium for Optimizing the Surgical Treatment of Rectal Cancer. Extended intervals after neoadjuvant therapy in locally advanced rectal cancer: the key to improved tumor response and potential organ preservation. *J Am Coll Surg* 2015;221:430–40.
16. Lefevre JH, Mineur L, Kotti S, *et al.* Effect of interval (7 or 11 weeks) between neoadjuvant radiochemotherapy and surgery on complete pathologic response in rectal cancer: a multicenter, randomized, controlled trial (GRECCAR-6). *J Clin Oncol* 2016;34:3773–80.
17. Roh MS, Colangelo LH, O'Connell MJ, *et al.* Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol* 2009;27:5124–30.
18. Onaitis MW, Noone RB, Fields R, *et al.* Complete response to neoadjuvant chemoradiation for rectal cancer does not influence survival. *Ann Surg Oncol* 2001;8:801–6.
19. Hiotis SP, Weber SM, Cohen AM, *et al.* Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients. *J Am Coll Surg* 2002;194:131–5.
20. Bosset JF, Calais G, Mineur L, *et al.* Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for

rectal cancer: preliminary results—EORTC 22921. *J Clin Oncol* 2005;23:5620–7.
21. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. *Br J Surg* 2012;99:918–28.
22. Habr-Gama A, Perez RO, Nadalin W, *et al.* Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg* 2004;240:711–17.
23. Habr-Gama A, Perez RO, Proscurshim I, *et al.* Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. *J Gastrointest Surg* 2006;10:1319–28.
24. Habr-Gama A, Sao Juliao GP, Gama-Rodrigues J, *et al.* Baseline T classification predicts early tumor regrowth after nonoperative management in distal rectal cancer after extended neoadjuvant chemoradiation and initial complete clinical response. *Dis Colon Rectum* 2017;60:586–94.
25. Martens MH, Maas M, Heijnen LA, *et al.* Long-term outcome of an organ preservation program after neoadjuvant treatment for rectal cancer. *J Natl Cancer Inst* 2016;108:pii:djw171.
26. Maas M, Beets-Tan RG, Lambregts DM, *et al.* Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol* 2011;29:4633–40.
27. Renehan AG, Malcomson L, Emsley R, *et al.* Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. *Lancet Oncol* 2016;17:174–83.
28. de Jong EA, ten Berge JC, Dwarkasing RS, Rijkers AP, van Eijck CH. The accuracy of MRI, endorectal ultrasonography, and computed tomography in predicting the response of locally advanced rectal cancer after preoperative therapy: a metaanalysis. *Surgery* 2016;159:688–99.
29. Hanly AM, Ryan EM, Rogers AC, *et al.* Multicenter evaluation of rectal cancer reimaging post neoadjuvant (MERRION) therapy. *Ann Surg* 2014;259:723–7.
30. Zhao RS, Wang H, Zhou ZY, Zhou Q, Mulholland MW. Restaging of locally advanced rectal cancer with magnetic resonance imaging and endoluminal ultrasound after preoperative chemoradiotherapy: a systemic review and meta-analysis. *Dis Colon Rectum* 2014;57:388–95.
31. van der Paardt MP, Zagers MB, Beets-Tan RG, Stoker J, Bipat S. Patients who undergo preoperative chemoradiotherapy for locally advanced rectal cancer restaged by using diagnostic MR imaging: a systematic review and meta-analysis. *Radiology* 2013;269:101–12.
32. Guillem JG, Ruby JA, Leibold T, *et al.* Neither FDG-PET nor CT can distinguish between a pathological complete response and an incomplete response after neoadjuvant chemoradiation in locally advanced rectal cancer: a prospective study. *Ann Surg* 2013;258:289–95.
33. Kristiansen C, Loft A, Berthelsen AK, *et al.* PET/CT and histopathologic response to preoperative chemoradiation therapy in locally advanced rectal cancer. *Dis Colon Rectum* 2008;51:21–5.
34. Nakagawa WT, Rossi BM, de O Ferreira F, *et al.* Chemoradiation instead of surgery to treat mid and low rectal tumors: is it safe? *Ann Surg Oncol* 2002;9:568–73.
35. Guastadisegni C, Colafranceschi M, Ottini L, Dogliotti E. Microsatellite instability as a marker of prognosis and response to therapy: a meta-analysis of colorectal cancer survival data. *Eur J Cancer* 2010;46:2788–98.
36. Kalady MF, Dejulius KL, Sanchez JA, *et al. BRAF* mutations in colorectal cancer are associated with distinct clinical characteristics and worse prognosis. *Dis Colon Rectum* 2012;55:128–33.
37. Gonsalves WI, Mahoney MR, Sargent DJ, *et al.* on behalf of the Alliance for Clinical Trials in Oncology. Patient and tumor characteristics and *BRAF* and *KRAS* mutations in colon cancer, NCCTG/Alliance N0147. *J Natl Cancer Inst* 2014;106:pii:dju106.
38. Shia J, Holck S, Depetris G, Greenson JK, Klimstra DS. Lynch syndrome–associated neoplasms: a discussion on histopathology and immunohistochemistry. *Fam Cancer* 2013;12:241–60.
39. McConechy MK, Talhouk A, Li-Chang HH, *et al.* Detection of DNA mismatch repair (MMR) deficiencies by immunohistochemistry can effectively diagnose the microsatellite instability (MSI) phenotype in endometrial carcinomas. *Gynecol Oncol* 2015;137:306–10.
40. Ribic CM, Sargent DJ, Moore MJ, *et al.* Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 2003;349:247–57.
41. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol* 2005;23:609–18.
42. Sargent DJ, Marsoni S, Monges G, *et al.* Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J Clin Oncol* 2010;28:3219–26.
43. Funkhouser WK Jr, Lubin IM, Monzon FA, *et al.* Relevance, pathogenesis, and testing algorithm for mismatch repair–defective colorectal carcinomas: a report of the association for molecular pathology. *J Mol Diagn* 2012;14:91–103.
44. Sepulveda AR, Hamilton SR, Allegra CJ, *et al.* Molecular biomarkers for the evaluation of colorectal cancer: guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology. *Arch Pathol Lab Med* 2017;141:625–57.
45. Davies H, Bignell GR, Cox C, *et al.* Mutations of the *BRAF* gene in human cancer. *Nature* 2002;417:949–54.
46. Venderbosch S, Nagtegaal ID, Maughan TS, *et al.* Mismatch repair status and *BRAF* mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. *Clin Cancer Res* 2014;20:5322–30.
47. Tran B, Kopetz S, Tie J, *et al.* Impact of *BRAF* mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. *Cancer* 2011;117:4623–32.
48. Zhu L, Dong C, Cao Y, *et al.* Prognostic role of *BRAF* mutation in stage II/III colorectal cancer receiving curative resection and adjuvant chemotherapy: a meta-analysis based on randomized clinical trials. *PLoS One* 2016;11:e0154795.
49. Van Cutsem E, Kohne CH, Lang I, *et al.* Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor *KRAS* and *BRAF* mutation status. *J Clin Oncol* 2011;29:2011–19.
50. Vaughn CP, Zobell SD, Furtado LV, Baker CL, Samowitz WS. Frequency of *KRAS, BRAF,* and *NRAS* mutations in colorectal cancer. *Genes Chromosomes Cancer* 2011;50:307–12.
51. Gong J, Cho M, Fakih M. *RAS* and *BRAF* in metastatic colorectal cancer management. *J Gastrointest Oncol* 2016;7:687–704.
52. Vakiani E, Yaeger R, Brooke S, Zhou Y, Klimstra DS, Shia J. Immunohistochemical detection of the *BRAF* V600E mutant protein in colorectal neoplasms. *Appl Immunohistochem Mol Morphol* 2015;23:438–43.
53. Le DT, Uram JN, Wang H, *et al.* PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015;372:2509–20.
54. Diaz L, Marabelle A, Kim TW, *et al.* Efficacy of pembrolizumab in phase 2 KEYNOTE-164 and KEYNOTE-158 studies

of microsatellite instability high cancers. *Ann Oncol* 2017;28(suppl 5):v122–41.
55. Diaz LA, Marabelle A, Delord JP, *et al.* Pembrolizumab therapy for microsatellite instability high (MSI-H) colorectal cancer (CRC) and non-CRC [abstract 3071]. *J Clin Oncol* 2017;35:. [Available online at: https://meetinglibrary.asco.org/record/144822/abstract; cited 8 June 2018]
56. Overman MJ, McDermott R, Leach JL, *et al.* Nivolumab in patients with metastatic DNA mismatch repair–deficient or microsatellite instability–high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol* 2017;18:1182–91.
57. Overman MJ, Lonardi S, Wong KYM, *et al.* Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair–deficient/microsatellite instability–high metastatic colorectal cancer. *J Clin Oncol* 2018:36:773–9.
58. de Jong MC, Pulitano C, Ribero D, *et al.* Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann Surg* 2009;250:440–8.
59. de Jong MC, van Vledder MG, Ribero D, *et al.* Therapeutic efficacy of combined intraoperative ablation and resection for colorectal liver metastases: an international, multi-institutional analysis. *J Gastrointest Surg* 2011;15:336–44.
60. Ruers T, Van Coevorden F, Punt CJ, *et al.* Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. *J Natl Cancer Inst* 2017;109:.
61. Ruers T, Punt C, Van Coevorden F, *et al.* Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). *Ann Oncol* 2012;23:2619–26.
62. Sharma RA, Van Hazel GA, Morgan B, *et al.* Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil, and leucovorin chemotherapy. *J Clin Oncol* 2007;25:1099–106.
63. Wasan HS, Gibbs P, Sharma NK, *et al.* on behalf of the FOXFIRE trial investigators, SIRFLOX trial investigators, and FOXFIRE-Global trial investigators. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. *Lancet Oncol* 2017;18:1159–71.
64. Hendlisz A, Van den Eynde M, Peeters M, *et al.* Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol* 2010;28:3687–94.
65. van Hazel GA, Pavlakis N, Goldstein D, *et al.* Treatment of fluorouracil-refractory patients with liver metastases from colorectal cancer by using yttrium-90 resin microspheres plus concomitant systemic irinotecan chemotherapy. *J Clin Oncol* 2009;27:4089–95.
66. Gray BN, Burton MA, Kelleher DK, Anderson J, Klemp P. Selective internal radiation (SIR) therapy for treatment of liver metastases: measurement of response rate. *J Surg Oncol* 1989;42:192–6.
67. Virdee PS, Moschandreas J, Gebski V, *et al.* Protocol for combined analysis of FOXFIRE, SIRFLOX, and FOXFIRE-Global randomized phase III trials of chemotherapy +/– selective internal radiation therapy as first-line treatment for patients with metastatic colorectal cancer. *JMIR Res Protoc* 2017;6:e43.
68. Riaz A, Lewandowski RJ, Kulik LM, *et al.* Complications following radioembolization with yttrium-90 microspheres: a comprehensive literature review. *J Vasc Interv Radiol* 2009;20:1121–30.
69. de Jong MC, van Dam RM, Maas M, *et al.* The liver-first approach for synchronous colorectal liver metastasis: a 5-year single-centre experience. *HPB (Oxford)* 2011;13:745–52.
70. Sinicrope FA, Mahoney MR, Yoon HH, *et al.* Analysis of molecular markers by anatomic tumor site in stage III colon carcinomas from adjuvant chemotherapy trial NCCTG N0147 (Alliance). *Clin Cancer Res* 2015;21:5294–304.
71. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. *Nature* 2012;487:330–7.
72. Guinney J, Dienstmann R, Wang X, *et al.* The consensus molecular subtypes of colorectal cancer. *Nat Med* 2015;21:1350–6.
73. Tejpar S, Stintzing S, Ciardiello F, *et al.* Prognostic and predictive relevance of primary tumor location in patients with *RAS* wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. *JAMA Oncol* 2016;:[Epub ahead of print].
74. Zhang Y, Ma J, Zhang S, *et al.* A prognostic analysis of 895 cases of stage III colon cancer in different colon subsites. *Int J Colorectal Dis* 2015;30:1173–83.
75. Petrelli F, Tomasello G, Borgonovo K, *et al.* Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. *JAMA Oncol* 2016;:[Epub ahead of print].
76. Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V. The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. *Eur J Cancer* 2017;70:87–98.
77. Venook AP, Niedzwiecki D, Lenz HJ, *et al.* Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with *KRAS* wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. *JAMA* 2017;317:2392–401.
78. Venook AP, Niedzwiecki D, Innocenti F, *et al.* Impact of primary (1°) tumor location on overall survival (os) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): analysis of CALGB/SWOG 80405 (Alliance) [abstract 3504]. *J Clin Oncol* 2016;34:. [Available online at: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.3504; cited 8 June 2018]